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Diet in the treatment of ADHD in children—A systematic review of the literature

MAREN JOHANNE HEILSKOV RYTTER, LOUISE BELTOFT BORUP ANDERSEN, TINE HOUMANN, NIELS BILENBERG, ALLAN HVOLBY, CHRISTIAN MØLGAARD, KIM F. MICHAELSEN, LOTTE LAURITZEN

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Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric conditions in childhood. Dietary changes have been suggested as a way of reducing ADHD symptoms. *Aims:* To provide an overview of the evidence available on dietary interventions in children with ADHD, a systematic review was carried out of all dietary intervention studies in children with ADHD. *Methods:* Relevant databases were searched in October 2011, with an update search in March 2013. The studies included describe diet interventions in children with ADHD or equivalent diagnoses measuring possible changes in core ADHD symptoms: inattention, hyperactivity and impulsivity. *Results:* A total of 52 studies were identified, some investigating whether ADHD symptoms can improve by *avoiding* certain food elements (20 studies), and some whether certain food elements may *reduce* ADHD symptoms (32 studies). *Conclusion:* Elimination diets and fish oil supplementation seem to be the most promising dietary interventions for a reduction in ADHD symptoms in children. However, the studies on both treatments have shortcomings, and more thorough investigations will be necessary to decide whether they are recommendable as part of ADHD treatment.

• *ADHD, Dietary intervention, Review.*

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequent psychiatric conditions in childhood. It is caused by a combination of genetic and environmental factors, and symptoms vary within and between patients. Not all children with ADHD benefit from the standard pharmaceutical treatment: some experience side-effects, and there is concern about the long-term effects of the drugs on children (1, 2). Dietary changes have therefore been investigated for decades as a way of reducing symptoms in children with ADHD (3) (Fig. 1). The dietary changes that have been suggested as potential treatments of ADHD in children fall into two groups:

- 1) Dietary interventions that *remove* elements from the diet, elimination diets;
- 2) Dietary interventions that *increase* the intake of certain nutrients.

The *removal* of elements from the diet (the so-called elimination diets) is based on the idea that some children may have behavioural changes when exposed to certain food items. These intervention studies fall into three categories: artificial food colorants and other additives, sugar, and “Few Foods Diets”.

The research within *artificial food colorants and other additives* began in the 1970s. It was hypothesized that a diet without natural salicylates and artificial food colorants, the Kaiser Permanente diet, also known as the K-P diet or the Feingold diet, could improve symptoms in children with “hyperactivity” or “minimal brain dysfunction” (4).

A possible effect of *sugar and artificial sweeteners* has been a focus among parents who report that their children get “hyperactive” after eating a lot of sugar. A few observational studies have found that sugar ingestion was related to ADHD symptoms in children and adolescents

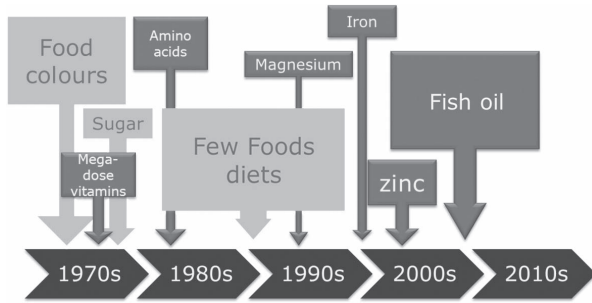


Fig. 1. Timeline: Focus of dietary interventions in relation to attention-deficit/hyperactivity disorder (ADHD). The arrow indicates when the various dietary components first became a focus area in ADHD research. The size of the boxes represents the number of studies performed within the field, and the color of the boxes the overall type of intervention. Light grey: food elements hypothesized to be recommended for removal from diet in order to decrease ADHD symptoms, and dark grey: food elements hypothesized to have a beneficial effect on ADHD symptoms when added to the diet.

(5, 6). The question is whether this “hyperactivity” is caused by the sugar, or by the circumstances often associated with a high sugar intake (birthday parties, holidays etc.). This may be particularly relevant in the case of children with ADHD, who often have difficulties in unstructured settings with many people. The widely used artificial sweetener aspartame has also been hypothesized as a problem in relation to ADHD.

Apart from sugar and artificial food colorants, it has been suggested that some children with ADHD could be sensitive to other food items, and that these specific food items vary from child to child (7). Few Foods Diets eliminate all but a few food items from the diet for a period. The diet typically consists of two types of meat, two sources of carbohydrates, two vegetables, two fruits, oil and water (8). Children are identified as “diet sensitive” if they show improvement after a few weeks on this type of diet. If so, food items are re-introduced in a controlled way to identify any specific food causing the child to react. This can be followed by random blinded challenges in which the foods that the child was found to react to were given disguised in other foods or in capsules. The overall idea is to identify the food items to be avoided in each specific case and thus design an individual diet for future use.

The rationale for the dietary interventions that *increase* the intake of certain nutrients are that children with ADHD could have deficiencies in these nutrients, either because of a low intake or because of a higher requirement. The nutrients in focus have been certain amino acids, essential fatty acids, vitamins and minerals.

The interest for *amino acids* was raised because the monoaminergic neurotransmitters, dopamine, serotonin

and norepinephrine, which are involved in the symptoms of ADHD, are synthesized from the amino acid precursors, phenylalanine, tyrosine and tryptophan (9). Thus, it has been suggested that supplements with these amino acids might help children with ADHD. In contrast, concerns have been raised that intake of phenylalanine via the artificial sweetener aspartame could increase symptoms in children with ADHD (10).

The interest in *essential fatty acids* in relation to ADHD began in 1981 (11), where the first studies focused on supplements of n-6 fatty acids from vegetable oils, but the main focus in this field has been the long-chain n-3 fatty acids (n-3 LCPUFA): docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish oil. The n- nomenclature indicates the location of the double bond in the carbon chain of the fatty acid, which is preserved during metabolism and is essential for the effects. DHA has been shown to play an important role in the structure and function of the brain (12). Studies in rats have shown that deficiencies in n-3 fatty acids, as well as supplementation with fish oil, affect levels of monoaminergic neurotransmitters (13). Lower blood levels of DHA have been observed in children with ADHD as well as associations between severe ADHD symptoms and low DHA concentrations (14, 15). Maternal fish oil supplementation during lactation has been associated with offspring attention and physical activity both in animal and human studies (16, 17).

When it comes to *vitamins*, B vitamins, especially B6 (pyridoxine), B9 (folate) and vitamin B12 (cobalamin), are all involved in the synthesis of monoaminergic neurotransmitters as well as in the metabolism of fatty acids (18). Deficiencies may therefore have negative consequences for cognitive functions. Vitamin C has also been used as a supplement in studies on ADHD, presumably based on its anti-oxidative effects, which may protect n-3 LCPUFA or oxidation in the brain in general, or the fact that it improves iron absorption. Carnitine is an ammonium compound with vitamin-like properties, which is provided by the diet or synthesized from lysine and methionine. Carnitine is essential for the transport of fatty acids. Supplementation with carnitine has been found to reduce ADHD-like symptoms in children with fragile X syndrome (19) and it has therefore been suggested that it may have a beneficial effect on children with ADHD.

The *minerals* zinc, iron and magnesium have all been suggested as potentially relevant supplements to children with ADHD. Zinc is involved in the synthesis of monoaminergic neurotransmitters. Deficiency in these minerals, specifically zinc and iron, is known to cause cognitive impairment in children (20, 21). Observational studies have furthermore found that children with ADHD have a lower status of these minerals (22–24). It has been proposed that children with ADHD may have a

different metabolism of especially zinc, and also that zinc status could modify the effect of factors like fatty acids (25). Iron deficiency has been suggested to be involved in restless legs syndrome (26), which shares some features with ADHD, and it has therefore been hypothesized that iron deficiency could also play a role in ADHD. Moreover, iron status may also influence the metabolism of essential fatty acids (27).

This broad systematic review aims to assess the “state of the art” of all the proposed dietary interventions, in order to qualify recommendations and future research.

Materials and methods

The review was performed in accordance with a pre-defined but unpublished protocol describing the aim, search strategy, inclusion and exclusion criteria, and the methods used to evaluate the studies.

Strategy of search and selection of literature

Literature search was carried out on 3 October 2011 and updated on 11 March 2013. The databases PubMed, Web of Science, PsycINFO and the Cochrane Library were searched for a combination of relevant words about diet and ADHD (Fig. 2), and the reference lists of the papers

- 1: "Food" (mesh) OR "diet" (mesh) OR "diet therapy" (mesh) OR "nutrition disorders" (mesh)
- 2: "micronutrients" (mesh) OR "trace elements" (mesh) OR "zinc" (mesh) OR "Magnesium" (mesh) OR "magnesium deficiency" (mesh) OR "Iron" (mesh) OR "iron deficiency anemia" (mesh) OR "copper" (mesh) OR "calcium" (mesh) OR "Niacin" (mesh) OR "vitamin B 12" (mesh) OR "Dietary Supplements" (mesh) OR "vitamin D" (mesh) OR "deficiency" (mesh)
- 3: "Lipids" (mesh) OR "fatty acids, unsaturated" (mesh) OR "Fatty Acids, essential" (mesh) OR "Fish oils" (mesh) OR "fatty acids" (mesh) OR "carnitine" (mesh)
- 4: "Milk, Human" (mesh) OR "Breastfeeding" (Mesh)
- 5: "probiotics" (mesh) OR "candida" (mesh)
- 6: "Hypersensitivity" (mesh) OR "Allergy and Immunology" (mesh) OR "immunoglobulins" (mesh), "salicylates" (mesh) OR "Milk" (mesh) OR "Glutens" (mesh) OR "Caseins" (mesh)
- 7: "food additives" (mesh) OR "flavoring agents" (mesh) OR "food preservatives" (mesh) OR "food coloring agents" (mesh) OR "Sweetening agents" (mesh)
- 8: "Dietary carbohydrates" (mesh)
- 9: "Amino acids" (mesh)
- 10: "Ketogenic diet" (mesh)
- 11: (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
- 12: "Attention Deficit and Disruptive Behavior Disorder" (mesh) OR "Hyperkinesia" (mesh) OR "Attention Deficit Disorders with Hyperreactivity" (mesh)
- 13: Search Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English, Danish, All Child: 0-18 years
- 14: #11 AND #12 AND #13
- 15: Food* OR Diet* OR nutrition* OR malnutrition
- 16: zink* OR iron* OR magnesium* OR copper* OR Calcium* OR vitamin* OR micronutrient*
- 17: "fatty acids" OR EFA OR DHA OR omega-3 OR omega-6 OR carnitine
- 18: breastfeeding
- 19: Probiotic* OR candida OR microbiota OR yeast
- 20: hyperreactivity OR allergy OR salicylates OR Feingold OR "Kaiser Permanente diet" OR "KP diet" OR milk OR casein OR gluten OR "oligoantgenic diet" OR "oligoallergenic diet" OR "few foods diet" OR "elimination diet"
- 21: "food additive*" OR "food colour*" OR color* OR flavour* OR preservative*
- 22: sugar OR sucrose
- 23: "amino acid*"
- 24: "ketogenic diet"
- 25: (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)
- 26: ADHD OR hyperactivity OR inattention OR impulsivity OR "Attention Deficit Hyperactivity Disorder" OR "Minimal Brain Dysfunction"
- 27: Search Limits: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, English, Danish, All Child: 0-18 years
- 28: #25 AND #26 AND #27
- 29: Search Limits: published in the last 180 days
- 30: #25 AND #26 AND #28

Fig. 2. PubMed search strategy for the main search.

retrieved were examined for further relevant studies. The literature search and selection of papers were performed independently by two researchers (MJHR, LBBA). Diverging views on inclusion of papers were discussed and settled between all authors of this review. Figure 3 gives an overview of the search and selection process.

Inclusion criteria

EXPOSURE AND STUDY TYPE

We included literature published in English describing controlled/uncontrolled and blinded/open intervention studies, evaluating the effect of a change in diet or intake of a nutritional supplement on ADHD symptoms. Both parallel and crossover designs were allowed, and unless otherwise stated, the term “randomized controlled trial” (RCT) is used to refer to the parallel studies.

PARTICIPANTS

The participants of the included studies had to be children (0–18 years) with a diagnosis of ADHD or older diagnoses equivalent to ADHD. For recent studies, a diagnosis of ADHD based on *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) or hyperkinetic disorder based on the *International Classification of Diseases-10* (ICD-10) was required, but older studies with an equivalent diagnosis, e.g. “minimal brain dysfunction”, were included as well. ADHD should be the main diagnosis but co-morbidities were accepted. No

restrictions were imposed as to whether the children received medication. Studies with fewer than 10 subjects were excluded.

OUTCOMES

Included studies should report change in core symptoms of ADHD (hyperactivity, impulsivity and inattention) as an outcome, preferably based on validated scales or tests. The scales used were the Conners Scales or the ADHD Rating Scale, but we also accepted studies using locally developed scales, as long as their purpose was to assess ADHD core symptoms. Studies that used tests to assess hyperactivity, impulsivity and inattention were also included. These comprised the Continuous Performance Test (CPT), Matching Familiar Figures Test, Draw-a-Line-Slowly Test, Zero Input Tracking Analyzer and Auxiliary Distraction Task, Freedom from Distractibility Index of the Wechsler Intelligence Scale for Children, among others.

Results

A total of 52 studies met the inclusion criteria. The most frequent reasons for excluding studies were that the study included children not diagnosed with ADHD or similar conditions or did not report change in ADHD core symptoms, or had fewer than 10 participants. Due to the heterogeneous nature of the interventions, participants and outcomes, it was decided not to attempt to perform a

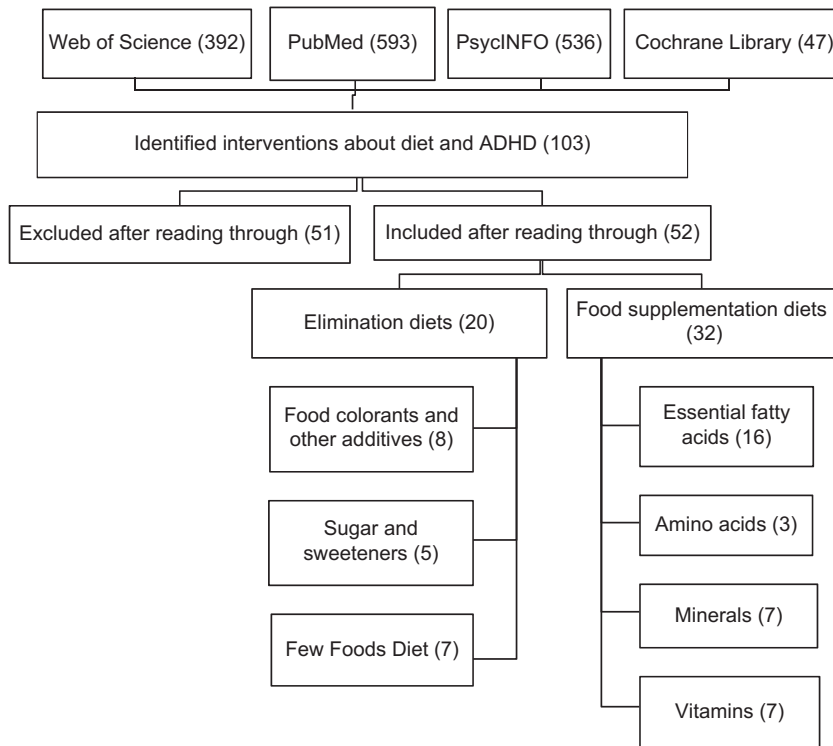


Fig. 3. Outline of studies accessed and included in the review. One study (61) is included both in the section about essential fatty acids and about vitamins.

meta-analysis, but instead report the data as a systematic review, where we took the size and methodological approach of the studies into account. Others have performed meta-analyses, but heterogeneity was high between studies, making it questionable whether the studies were indeed suitable for pooling (28–31).

The studies fall into two groups: 1) dietary interventions that *remove* elements from the diet (20 studies) and 2) dietary interventions that *increase* the intake of certain nutrients (32 studies).

Elimination diets

ARTIFICIAL FOOD COLORANTS AND OTHER ADDITIVES

The studies assessing the effect of artificial food colorants were either *diet studies*, assessing whether ADHD symptoms in children improved on a diet without artificial colours (K-P diet), or *challenge studies*, evaluating whether children's symptoms worsened when exposed to artificial food colorants (Table 1).

Of the six studies describing the effect of the K-P diet, two were uncontrolled studies (preceding challenge studies) (32, 33) and four had a randomized double-blinded crossover design, in which the children followed a K-P diet and an equally restrictive control diet for 3–4 weeks each (34–37). Four *challenge studies* assessed the effect of giving artificial food colorants by randomized double-blinded crossover challenges (32, 33, 38, 39). In these studies, children followed a diet without artificial food colorants but were given a cookie every day, which on some days contained artificial food colorants.

Both uncontrolled diet studies reported improved symptoms after the K-P diet, whereas the results of the controlled studies were mixed. None of the diet RCTs found a significant effect that was consistent among parents, teachers and clinical tests, but most did find an effect in the parent's ratings. Three of the challenge studies found some deterioration in behaviour of the children when exposed to artificial food colorants (32, 33, 38), whereas one study did not find any effect (39). Many of these studies found differences in the effect evaluated by parents and teachers. Overall, the studies do not provide any clear and convincing results.

There are a number of limitations to the studies on artificial food colorants. First, they all had few participants: the largest included 46 children. Besides, all studies but one are more than 30 years old, so children included are likely to differ from the children fulfilling today's ADHD criteria. Some studies tested a mix of additives, whereas one tested only tartrazine (2 mg). It has, however, been suggested that the realistic daily intake of an American child is up to 150 mg of tartrazine (40), so the study may have overlooked a relevant effect. Finally, all the challenge studies used chocolate cookies as a vehicle for the food colorants. As later and more

extensive Few Foods Diets studies have found that some children reacted to cocoa and wheat, this may have blurred any possible effect of the artificial food colorants.

The ambiguous results of the studies and their methodological limitations make it difficult to draw any firm conclusions regarding the effect of artificial food colorants in children with ADHD. However, two large studies carried out on a general population of children (41, 42) both found that normal children showed increase in ADHD-like behaviour after receiving a mix of artificial colorants, so-called "azo-dyes", together with the preservative sodium benzoate. The reaction was not related to whether the child was known hyperactive or allergic, but seemed linked to genetic polymorphisms in the metabolism of histamine (43). As a result, the European Union has passed a law stating that foods containing "azo-dyes" should bear a warning label stating that they may have adverse effects on children's behaviour and attention (44).

Four meta-analyses have been carried out on this issue, the most recent published in 2013 (28, 29, 45, 46). All conclude that artificial food colorants have small, but statistically significant adverse effects on ADHD symptoms in some children, but that this is based on studies of limited quality.

SUGAR AND ARTIFICIAL SWEETENERS

Five crossover RCTs have assessed the acute effect of sugar and aspartame on children with ADHD or equivalent diagnoses (Table 2). One of the RCTs examined aspartame vs. control (10), one compared sugar and saccharine (47), two compared sugar vs. aspartame (48, 49), and the last tested both sugar and aspartame vs. saccharine (50). Overall, these studies found no change in core ADHD symptoms with either sugar or aspartame; although one found an increase in inattention with sugar relative to both saccharin and aspartame (50).

The studies are relatively old, had few participants and only assessed the effect of short-term exposure. The studies may therefore have missed small effects, effects that only occurred in a minority of children, or after long-term exposure. Furthermore, two of the studies compared two food components with proposed harmful effects (sugar and aspartame), so it may not be possible to evaluate the effect of any of these compounds. At present, the literature does not support the theory that sugar, or any other sweetener, causes symptoms of ADHD in children.

FEW FOODS DIETS

Seven studies have attempted to test Few Foods Diets in children with ADHD (Table 3); only one of them, however, in a double-blinded RCT design under controlled conditions (51). This study was performed as a crossover study in hospitalized children who received all their food in the Few Foods Diet or a comparison diet from the

Table 1. Studies assessing the effect of artificial food colorants on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

Reference	n, age, sex, diagnosis [†]	Intervention	Outcome measure	Results (rater)
Diet studies				
Kaplan et al., 1989 (37)	24, 3–6 years, 100% boys, ADD-H (a,c)	Diet with no artificial colorants vs. control for 4 weeks. All food provided	Abbreviated Conners Scales; Motor Accuracy Test of the Southern California Sensory Integration Test; Matching Familiar Figures Test; Memory for Colors test; Visual Attention Span test; Detroit Test of Learning Aptitude; Anima House test from the Wechsler Preschool and Primary Scale of Intelligence	Improvement on diet without artificial food colours (P); No effect (T – only half of the children evaluated); Test: most children not able to complete the tests
Eich et al., 1979 (36)	16, age and gender not given, MBD (a)	K-P diet vs. control diet for 4 weeks each	Conners Scales; The Beery Buchtenia Test of Visual Motor Integration; Porteus Maze Test; Digit span subtest of WISC; Quick Neurological Screening test	Diet improved Conners score (P, not T); No improvement in tests
Hanley et al., 1978 (35)	46, 3–12 years, 100% boys, hyperkinetic reaction of childhood (a,b)	K-P diet vs. control diet for 3 weeks each. All food provided	Conners Scales; Class-room observation; Laboratory observation; WISC; Wide Range Achievement Test Reading; Finger-tapping speed; Kinetic Steadiness; Grooved pegboard	Diet improved Conners scores (P, not T); No improvement in class-room or laboratory observation or in any tests
Goyette et al., 1978* (33)	16, 4–11 years, gender not given, hyperactive (d)	K-P diet	Conners Scales; Zero Input Tracking Analyzer and Auxiliary Distraction Task	Improvement on Conners Scales (P and T) with diet compared with before diet; Results of tests not reported
Levy et al., 1978* (32)	22, 4–8 years, 86% boys, hyperactive (a)	K-P diet	Conners Scales; Sprague Ballistographic Chair; CPT; Draw-a-line Slowly test; Motor-Accuracy and Figure-Ground subsets of the Jean Ayres test; Auditory Sequential Memory task from Illinois Test of Psycho-Linguistic Ability; Animal House from Wechsler Preschool and Primary Scale of Intelligence; Mazes subtests from the WISC	Improvement on Conners Scales (P, not T) with diet compared with before diet; No effects on any tests reported
Conners et al., 1976 (34)	15, 6–12 years, gender not given, hyperkinetic reaction of childhood (a)	K-P diet vs. control diet for 4 weeks each	Conners Scales; Clinical Global Impression-Improvement (CGI-I)	Improvement on Conners Scales (P, not T); CGI-I improved more with K-P diet than with placebo diet (psychiatrist)
Challenge studies				
Adams, 1981 (39)	18, 4–11 years, 83% boys, hyperactive (d)	Mixed colorants (26 mg) (Yellow no. 5, Red no. 3, Red no. 40, Yellow no. 7)	Numerical Memory and Draw-a-Child subtests from McCarthy Scales; Visual-memory sequenced subtest from the Illinois Test of Psycho-linguistic Ability; Peabody Picture Vocabulary Test; "Activity Room" observation; Developmental Test of Visual-motor Integration	No difference with tests (O)
Williams et al., 1978 (38)	28, 5–12 years, gender not given, hyperactive (a)	Unspecified mixed colorants (dose not stated) both with and without medicine	Conners Scales	Colorants deteriorated ADHD symptoms on Conners Scales, independent of medicine (P and T)

Levy et al., 1978* (32)	RCT crossover	22, 4–8 years, 86% boys, hyperactive (a)	Tartrazine (2 mg)	Conners Scales; Sprague Ballistographic Chair; CPT; Draw-a-line Slowly test; Motor-Accuracy and Figure-Ground subsets of the Jean Ayres test; Auditory Sequential Memory task from Illinois Test of Psycho-Linguistic Ability; Animal House from Wechsler Preschool and Primary Scale of Intelligence; Mazes subsets from the WISC	No difference on Conners Scales (P and T) or with tests (observer); Subgroup: effect in youngest children (P, not T)
Goyette et al., 1978* (33)	RCT crossover	16, 4–11 years (part 1)+ 13, 3–10 years (part 2), gender not given, hyperactive (d)	Unspecified mixed colorants (dose not stated)	Conners Scales (part 1: 3 times weekly; part 2: 3 h after ingestion); Zero Input Tracking Analyzer and Auxiliary Distraction Task	Part 1: No significant difference on Conners Scales (P and T), subgroup analysis: effect in youngest children; Part 2: Deterioration with food colorants on Conners Scales (P); No effect with tests (O)

RCT, randomized controlled trial; K-P diet, Kaiser Permanente diet; P, parents; T, teachers; O, observer; ADD-H, attention-deficit disorder with hyperactivity; MBD, minimal brain dysfunction; CPT, Continuous Performance Test.

*Studies listed both under diet studies and under challenge studies.

†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

hospital kitchen. Two open RCTs compared the Few Foods Diet with no treatment (52) or dietary instruction on “healthy food” (53). Four uncontrolled diet studies (8, 54–56) were carried out, of which all but one (54) were followed by double-blinded re-introduction challenges in the children who responded to the initial diet.

The double-blinded crossover RCT found a significant improvement of ADHD symptoms with the Few Foods Diet, and 24% of the children were found to improve during the elimination diet period vs. only 4% in the control period (51). The two open RCTs also found improvement in ADHD symptoms, with response rates of 64–73% (52, 53). The four uncontrolled studies comparing children’s behaviour during the Few Foods Diet period with their behaviour before the introduction of the elimination diet also found a significant decrease in symptoms (8, 54–56). In the three studies that did random blinded challenges, the children had significantly more ADHD symptoms when given suspected foods than when given control food (8, 55, 56). There was no clear pattern in the types of food items causing the reactions.

The studies of Few Foods Diets have serious limitations. First, the apparent effect of the diet in the uncontrolled studies could be explained by factors other than the diet itself (e.g. the beliefs of the parents or the change of home-setting structure that a strict diet warrants). Similarly, the lack of blinding in two of the controlled trials is a potential source of bias. On the other hand, it may be difficult to blind families to a diet that is restrictive and individually tailored to the child’s symptoms (53). Third, most studies included children of parents with a dietary interest (55), and only one study included children referred to a general child psychiatry clinic (51). The latter study was also the only truly blinded RCT, and it had the lowest proportion of responders. In the studies that included a double-blinded challenge phase, only a minority of the children completed the challenges (8, 55), either because they dropped out, or because the food they reacted to was not suitable for double-blinded challenge. The use of such a highly selected study groups limits the relevance of the results of the blinded challenges. Furthermore, a plausible biological explanation for the apparent effect of these diets is lacking, as this does not seem to be explainable by any known allergic mechanism as earlier suggested.

In spite of these limitations, it is intriguing that all seven studies found significant effects on core ADHD symptoms. Beneficial effects were also seen in the studies that included a double-blinded challenge, indicating that this might not just be a placebo effect.

Two recent meta-analyses have analysed the effects of elimination diets. One concluded that restrictive diets may benefit some children with ADHD (28), the effect size being about one third of that of medication, and clinically relevant. However, this meta-analysis also

Table 2. Studies assessing the effect of sugar or aspartame on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

Reference	Design	n, age, sex, diagnosis [†]	Intervention	Outcome measure	Results (rater)
Shaywitz et al., 1994 (10)	RCT crossover	15, 5–13 years, 73% boys, ADD-H (d)	Aspartame (about 1.3 g*) vs. control (cellulose) for 2 weeks	Conners Scales; Multigrade Inventory scale; Matching Familiar Figures Test; Wisconsin Card Sorting test; the Children's Checking Task and the Airplane test	No significant difference on Conners Scales (P and T) or tests; Activity subscale at the multigrade Inventory (T) scale significant lower in placebo group
Wender & Solanto, 1991 (50)	RCT crossover (challenge)	17, 6–8 years, gender not given, ADD-H (a,b)	One sugar drink (35 g) vs. control (aspartame or saccharin)	CPT	Significantly increased inattention in test after sugar intake; No significant difference between the two controls
Milich & Pelham, 1986 (49)	RCT crossover (challenge)	16, 6–9 years, 100% boys, ADD-H (a,b)	One sugar drink (about 50 mg) vs. control (aspartame)	Conners Scales; Tests developed for occasion	No significant difference on Conners Scales (T) or tests
Wolraich et al., 1985 (48)	RCT crossover (challenge)	2 × 16, 7–12 years, 100% boys, hyperactive (a,b)	One sugar drink (about 61 mg*) vs. control (aspartame) both fasting and post-prandial	Undefined scales; CPT; Draw a Line Fast test; Draw a Line Slowly test; Match Familiar Figures test; Paired-associate Learning test; Accelerometer output	No significant difference on scales (O), tests or accelerometer output, irrespective of fasting or not
Gross, 1984 (47)	RCT crossover (challenge)	50, 5–7 years, 72% boys, hyperkinetic syndrome (d)	One sugar drink (75 g) vs. control (saccharin)	Scale made for the occasion rating behaviour	No significant difference (P)

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder with hyperactivity; CPT, Continuous Performance Test.

*Dose calculated based on child's weight.

[†]Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

included studies of children who followed diets without food colorants, and thus did not specifically assess the effect of Few Foods Diets. The most recent meta-analysis found that a large effect size in all included studies was reduced to an insignificant effect when looking only at assessments made by an independent blinded assessor (29).

Few Foods Diets may, however, even despite a significant effect, not be relevant in ordinary treatment. None of the studies assessed how well children accepted the diet. Following a diet is often described as laborious and disruptive to social life, and adherence is often poor (57). A restricted Few Foods Diet for a long period can become nutritionally inadequate, especially in growing children, and requires supervision by professionals (52). Few Foods Diets are not meant as treatment, but only as a method to identify diet-sensitive children. The actual treatment is the individually tailored diet designed after repeated challenges have identified which food items should be avoided. The entire reintroduction process is

estimated to last around a year (53) and call for substantial resources from families and the healthcare system. No studies followed the participants longer than 9 weeks, and no studies have assessed the effect of the final individual diet. Furthermore, it is not clear what specific foods the children typically react to, how restrictive the final diets needs to be, and whether the nutritional value of this diet is satisfactory.

Increasing intake of certain nutrients

AMINO ACIDS

Three small RCTs (Table 4) have assessed potential effects of supplementation with amino acids (10, 58, 59). The results of these studies did not show any effect of tyrosine or phenylalanine. The study testing tryptophan found an improvement in ADHD symptoms on the parent ratings, but not in the teacher ratings (58). At present, there is no evidence that children with ADHD benefit from amino acid supplementation, but more studies are needed to make firm conclusions.

Table 3. Studies assessing Few Foods Diets in children with attention-deficit/hyperactivity disorder (ADHD).

Reference	Design	n, age, sex, diagnosis [†]	Intervention	Outcome measure	Results (rater)
Pelsser et al., 2011 (53)	Open RCT	100, 4–8 years, 86% boys, ADHD (a)	5-week elimination diet vs. instructions on healthy diet	Conners and the ADHD rating scales	Significantly fewer symptoms with elimination diet on Conners and the ADHD rating scales (T and P); Improvement for 64% of children
Pelsser, Frankena, et al., 2009 (52)	Open RCT	27, 4–9 years, 81% boys, ADHD (a)	5-week elimination diet vs. waiting list	Conners and the ADHD rating scales	Significantly fewer symptoms with elimination diet on Conners and the ADHD rating scales (P and T); Improvement for 73% of children
Schmidt et al., 1997 (51)	RCT crossover	49, 6–12 years, 96% boys, ADHD (47 children) and/or conduct disorder 41 children (a)	9-week elimination diet vs. control diet	Conners Scales; CPT and PALT tests	Significantly fewer symptoms with elimination diet on Conners Scales (O, not T) or CPT and PALT tests; Improvement for 25% of children
Boris & Mandel 1994 (56)	Uncontrolled diet+ blind crossover challenge	26, 3–12 years, 73% boys, ADHD (a)	2-week diet → open challenge → blind random challenge	Conners Scales	Improvement with diet for 73% of children on Conners Scales (P); Significantly more symptoms with suspected foods in blind challenge
Carter et al., 1993 (8)	Uncontrolled diet+ blind crossover; Challenge	78, 3–12 years, 88% boys, ADHD (a)	3-week diet → open challenge → blind random challenge	Conners Scales; PALT and MFF test.	Improvement with diet for 76% of children on Conners Scales (P); Significantly more symptoms with suspected foods (P and O) and improved PALT and MFF test. test results
Egger et al., 1985 (55)	Uncontrolled diet+ blind crossover challenge	76, 2–15 years, gender not given, hyperkinetic syndrome or overactivity behavioural disturbance (a)	3-week diet → open challenge → blind random challenge	Conners Scales; Porteus maze test and MFF, accelerometer	Improvement with diet for 82% of children (P and O); Significantly more symptoms with suspected foods on Conners Scales (P and O) and Porteus maze test and MFF tests, but no change in accelerometer
Rapp, 1978 (54)	Uncontrolled diet	24, 5–16 years, gender not given, hyperactive (a)	1-week diet → open challenge	GCI	Improvement on diet for 50% of children on GCI (P)

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; GCI, Global Clinical Impression; PALT, Paired Associate Learning Test; MFF, Matching Familiar Figures Test; CPT, Continuous Performance Test; GCI, Global Clinical Impression.

[†]Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

ESSENTIAL FATTY ACIDS

We identified 16 studies investigating the effect of essential fatty acids supplementation on ADHD symptoms in children. Thirteen of these studies supplemented with fish oils containing n-3 LCPUFA (DHA and EPA) (60–72). Three studies used plant oil supplements providing linoleic acid (LA) and alpha-linolenic acid (ALA) (73–75) (Table 5). Six of the studies giving fish oil also supplemented with n-6 fatty acids, usually gamma-linolenic acid (GLA).

Overall, the plant oil interventions did not find any convincing beneficial effects on ADHD symptoms. One uncontrolled study supplementing with 400 mg/day of ALA for 3 months found a reduction in total hyperactivity score on parent rating scales, relative to before the intervention (74). However, a RCT (75) found no effect after 7 weeks of supplementation with 120 mg/day of ALA and 480 mg/day of LA. Only one small study (73) examined the effect of exclusive supplementation with n-6 fatty acids and did not find any effect.

Table 4. Studies assessing the effect of amino acids on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

Reference	Design	N, age, sex, diagnosis [†]	Intervention	Outcome measure	Results (rater)
Shaywitz et al., 1994 (10)	RCT crossover	15, 5–13 years, 73% boys, ADD (a)	Phenylalanine (as aspartame) 300 mg vs. control (cellulose) for 2 weeks	Conners and Multigrade Inventory scales; Matching Familiar Figures Test, Wisconsin Card Sorting test, the Children's Checking Task and the Airplane tests	No significant difference on Conners and multigrade Inventory scales (P or T) or the Matching Familiar Figures Test, Wisconsin Card Sorting test, the Children's Checking Task and the Airplane tests
Zametkin et al., 1987 (59)	RCT crossover	11, 6–12 years, 100% boys, ADD-H (a)	Phenylalanine, 400–700 mg* vs. control tablets for 2 weeks	Conners Scales; CGI, CPT	No significant difference on Conners Scales (P) or CGI and CPT tests
Nemzer et al., 1986 (58)	RCT crossover	14, 7–12 years, 79% boys, ADD (a,b)	Tyrosine, 4.2 g or tryptophan, 3 g* vs. control (lactose) each for 1 week	Conners Scales and, David's Hyperkinetic Scale; WISC-R	No significant difference on Conners Scales and, David's Hyperkinetic Scale with tyrosine (P and T) or WISC-R Subtest of Concentration and Impulsivity; Significant improvement on Conners Scales and, David's Hyperkinetic Scale with tryptophan (P, not T), but not in test

RCT, randomized controlled trial; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder; ADD-H, attention deficit disorder with hyperactivity, Swanson, Nolan and Pelham rating; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale; WISC-R, Wechsler Intelligence Scale for Children—Revised.

*Dose calculated based on child's weight.

[†]Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

In the fish oil supplementation trials, one of the two uncontrolled studies found a reduction in ADHD symptoms (64). However, the results from the 11 controlled RCTs are more ambiguous. One of the RCTs reported a significant difference in an overall ADHD symptom scale between the intervention and the control group (72), while the remaining 10 studies did not find any overall effect. However, three of them (62, 68, 69) did find a positive effect on one or more of the ADHD subscales, although not on the same subscales in all studies, and one (65) found a positive effect on the CPT.

The fish oil RCTs have four major limitations: frequent use of multiple testing, a relatively low number of participants, low doses of n-3 LCPUFA, and relatively short intervention periods. Multiple testing using many evaluation scales is seen because n-3 LCPUFA may affect ADHD symptom areas differently, but without correction for multiple testing it increases the risk of chance findings. Only four of the fish oil RCTs had ≥ 90 participants (68–70, 72) and detecting a possible effect of fish oil on ADHD symptoms may require the power of an even larger number of participants. Most of the studies have used lower doses than those generally used in fish oil research (typically 1–3 g/day of n-3 LCPUFA) (76). Only two of the RCTs gave >1 g/day of n-3 LCPUFA (66, 70), and five gave 0.5–1 g/day of n-3 LCPUFA (62, 63, 67, 68, 72). The interventions had a

duration from 4 to 26 weeks, and six of the studies lasted ≥ 15 weeks (60–62, 68–70, 72). Assuming that fish oil affects ADHD symptoms by incorporation into the brain, it may be expected to take some time before any effect occurs. The study showing an effect on overall ADHD-scale scores (72) and one of the studies with subscale effects (68) were among the four studies that had ≥ 90 participants, gave ≥ 500 mg/day of n-3 LCPUFA and lasted ≥ 15 weeks.

Most of the fish oil RCTs used plant oil as control (63, 65–68, 70, 72), and as mentioned above these oils have been used as the primary intervention in other studies (73–75). This seems contradictory, but as the plant oils are used in low doses and furthermore have not been shown to affect ADHD symptoms, this is not expected to blur the possible effect of fish oil. One study have used fish oil supplementation in combination with other fatty acids, vitamins and minerals (61) and caution should be taken to interpret these results together with the studies only intervening with fish oil. Three studies allowed participant to be on ADHD medication (62, 63) or gave fish oil as an adjunction to medication (60).

Overall, the evidence for a reduction in ADHD symptoms following supplementation with essential fatty acids from plant oils is sparse and showed no clear improvements in ADHD symptoms. Biologically, it is more plausible that supplementation with n-3 LCPUFA could

Table 5. Studies assessing the effect of essential fatty acids (fish oil in the top and plant oils in the bottom) on children with attention-deficit/hyperactivity disorder (ADHD).

Reference	Design	n, age, sex, diagnosis†	Intervention	Outcome measure	Results (rater)
Perera et al., 2012 (72)	RCT	98, 6–12 years, 73% boys, ADHD (a)	Fish oil and evening primrose oil (593 mg n-3 PUFA + 362 mg n-6 PUFA) vs. control (sunflower oil) for 26 weeks	Non-standardized scale	Fish and evening primrose oil significantly improved a non-standardized scale scores (P); Further improvement from 3 to 6 months
Milite et al., 2012 (70)	RCT	90, 7–12 years, 80% boys, ADHD (a,b)	EPA, 1109 mg + DHA, 108 mg or EPA, 264 mg + DHA, 1032 mg vs. control (sunflower oil) for 16 weeks	Conners Scales	No significant difference on Conners Scales (P)
Assareh et al., 2012 (71)	RCT	40, 6–12 years, 75% boys, ADHD (a)	DHA, 241 mg + EPA, 33 mg + n-6 PUFA, 180 mg vs. control (not given) for 10 weeks	ADHD Rating Scale	No significant difference on scales or subscales (P)
Manor et al., 2012 (69)	RCT	200, 6–13 years, 67% boys, ADHD (a,b)	DHA, 40 mg + EPA, 80 mg vs. control (cellulose) for 15 weeks, followed by 15 weeks DHA + EPA to all	Conners Scales	No significant overall difference, but significant improvement on 1 (restless/impulsive) of 8 Conners subscales (P, not T) and on 6 of 16 Conners subscales for subgroup with most symptoms; Uncontrolled part: Improvement on 2 of 8 Conners subscales (T) and on 3 of 8 (P)
Gustafsson et al., 2010 (68)	RCT	109, 7–12 years, mostly boys, ADHD combined type (a,b)	DHA, 2.7 mg + EPA, 500 mg vs. control (rapeseed oil and MCTFA) for 15 weeks	Conners Scales	No significant overall difference, but significant improvement on 1 (inattention) of 3 Conners subscales (T, not P) and significant improvement on overall Conners Scales score for subgroup with ADHD and conduct disorder (T, not P)
Johnson et al., 2009 (67)	RCT	75, 8–18 years, 85% boys ADHD(combined/inattentive type) (a,b)	DHA, 174 mg + EPA, 558 mg + GLA, 60 mg vs. control (olive oil) for 12 weeks, followed by 12 weeks of DHA, EPA + GLA to all	ADHD rating scale; GCI	No overall significant difference on ADHD rating scale scores (P), but significant improvement on GCI; >25% improvement for 26% of intervention children and 7% of control children Uncontrolled part: No difference between groups
Bélanger et al., 2009 (66)	RCT	37, 6–11 years, 69% boys, ADHD (a,b)	DHA, 300 mg + EPA, 730 mg* vs. control (sunflower oil) for 8 weeks, followed by 8 weeks of DHA + EPA to all	Conners Scales; SWAN scale; CPT	No significant difference on Conners and SWAN scales in RCT (P and T) or CPT; Uncontrolled part: No further improvement in intervention group, but improvement on 1 of 14 Conners subscales in former control group
Vaisman et al., 2008 (65)	RCT	83, 8–13 years, 75% boys, ADHD (a,b)	DHA, 125 mg + EPA, 125 mg vs. control (rapeseed oil) for 12 weeks	Conners Scales; CPT	No significant difference on Conners Scales (P), but improvement in CPT tests
Germano et al., 2007 (64)	Uncontrolled	31, 8 years on avg., 90% boys ADHD (a)	DHA, 0.9 g + EPA, 1.7 g* for 8 weeks	Conners Scale	Significant improvement in hyperactivity and inattention on Conners Scale (P)

(Continued)

Table 5. (Continued)

Reference	Design	n, age, sex, diagnosis ^f	Intervention	Outcome measure	Results (rater)
Hirayama et al., 2004 (63)	RCT	40, 6–12 years, 80% boys, ADHD (a)	Soya milk and bread with DHA, 514 mg + EPA, 100 mg vs. control (olive oil) for 8 weeks	DSM-IV questionnaire scales; Developmental test of visual–motor integration	No significant difference on DSM-IV questionnaire scales (P and T) and developmental test of visual–motor integration
Stevens et al., 2003 (62)	RCT	50, 6–13 years, ~88% boys, ADHD (a) + Essential fatty acid deficiency.	DHA, 480 mg + EPA, 80 mg + AA, 40 mg + GLA, 96 mg vs. control (olive oil) for 16 weeks	Impatience test and memory test; CPT and Development Test of Visual Perception	but significant improvement in CPT and Development Test of Visual Perception, tests in control group compared with fish oil group
Harding et al., 2003 (61)	Open uncontrolled	20, 7–12 years, gender not given AD/HD (a)	Mixed supplement with DHA, 120 mg + EPA, 180 mg or GLA, 45 mg or methylphenidate (duration not given)	Comners and DBD scales; CPT and Woodcock-Johnson Psycho-Educational Battery-Revised test	No significant difference on Comners and DBD scales, but significant improvement in 2 (conduct and attention) of 10 DBD subscales (P and T) and improvement in 1 (reaction time) of 7 CPT and Woodcock-Johnson Psycho-Educational Battery-Revised test parameters; Improvement in ADHD symptoms at the highest level of n-3 LCPUFA in the blood
Voigt et al., 2001 (60)	RCT	63, 6–12 years, mostly boys, ADHD (a)	DHA, 345 mg vs. control (not given) for 16 weeks	CPT	Improvement after supplement not stated; No significant difference between diet and medicine group in CPT tests;
Raz et al., 2009 (75)	RCT	63, 7–13 years, 60% boys, ADHD (a)	ALA, 120 mg + LA, 480 mg vs. control (vitamin C) for 7 weeks	Comners and CBCL scales; TOVA and Children's Color Trails tests	No significant difference on Comners and CBCL scales (P) or TOVA and Children's Color Trails tests
Joshi et al., 2006 (74)	Uncontrolled	30, 7 years on avg., 73% boys ADHD (a,b)	ALA, 400 mg for 12 weeks	DSM-IV questionnaire for ADHD and Comners Scales; TOVA tests	No significant difference on DSM-IV questionnaire for ADHD and Comners Scales (P and T) or TOVA tests
Arnold et al., 1989 (73)	RCT crossover	18, 6–12 years, 100% boys, ADHD (a,b)	LA, 2.8 g + GLA, 320 mg vs. control (paraffin) for 4 weeks	ADHD rating scale	Significant improvement on all tested ADHD rating scales (P)

RCT, randomized controlled trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, gamma-linolenic acid; ALA, alpha-linolenic acid; LA, linoleic acid; GCI, Global Clinical Impression; P, parents; T, teachers; O, observer; SWAN, Strengths and Weaknesses in ADHD and Normal Behaviors; DBD, Disruptive Behavior Disorders Rating Scale; TOVA, Test of Variables of Attention; CBCL, Child Behavior Checklist; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale.

*Dose calculated based on child's weight.

^fDiagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

decrease ADHD symptoms. Despite a number of relatively new and large intervention studies on this topic, there is still no firm evidence for the effect, and only one study found an overall effect.

The most recent systematic reviews and meta-analyses of the studies assessing the effect of LCPUFA on ADHD symptoms conclude that these fatty acids have a small (29) to modest (30) effects in the treatment of ADHD. One meta-analysis (30) found the effect to be mediated by n-3 LCPUFA, while another combined studies with n-3 and n-6 LCPUFA, and found that the small but significant effects remained even after excluding studies with simultaneously medication from the analysis (29).

By contrast, a Cochrane review concluded that there is little evidence that LCPUFA supplementation provides any benefit for the symptoms of ADHD in children and adolescents (31). A fourth meta-analysis calculated that, to show an effect, a study needs 330 participants and none of the current studies can match this (30).

VITAMINS

Seven studies (Table 6) investigated whether children with ADHD could benefit from vitamin supplementation. However, none of these studies investigated the use of multi-vitamin supplements in doses in line with the Recommended Daily Allowances (RDA), but all supplied

Table 6. Studies assessing the effect of vitamins on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

Reference	Design	n, age, sex, diagnosis†	Intervention	Outcome measure	Results (rater)
Abbasi et al., 2011 (82)	RCT	40, 7–13 years, 70% boys, ADHD (a)	Acetyl-L-carnitine, 1–3 g vs. methylphenidate for 6 weeks	ADHD rating scales	No significant difference on ADHD rating scales (P and T), but possibly fewer side-effects of methylphenidate
Arnold et al., 2007 (81)	RCT	112, 5–12 years, 74% boys, ADHD (a)	Acetyl-L-carnitine, 1–3 g vs. “identical soluble powder” for 16 weeks	Conners and CGI scales	No significant difference on Conners and CGI scales (P and T)
Harding et al., 2003 (61)	Open uncontrolled	20, 7–12 years, gender not given, ADHD (a)	Mix of various mega-doses vitamins+ fish oil, amino acids, probiotics vs. methylphenidate (duration not given)	CPT	No significant difference between treatments on CPT tests
Van Oudheusden & Scholte, 2002 (80)	RCT crossover	26, 6–13 years, 100% boys, ADHD (a)	L-Carnitine, 3 g ^a vs. identically looking and tasting drink for 8 × 3 weeks	Conners and CBCL scales	Significant improvement on Conners and CBCL scales (T and P)
Haslam et al., 1984 (79)	Uncontrolled+ RCT crossover	41 (7 in RCT), 7–11 years, both boys and girls (gender-ratio not given), ADD (a,b)	3-month open-phase with increasing doses of vitamin for all Followed by RCT with mega-doses vit. B3, B5, B6 and C vs. placebo capsule for 6 weeks.	Conners Scale	No significant difference on Conners Scales (P, T and O)
Brenner, 1982 (78)	RCT crossover	100, 4–15 years, gender not given, MBD (a)	Mega-dose vit. B1, B5, B6 or control (lactose) for 3 days each	No scales used	Tendency towards improvement on days with one of the vitamins (mostly to vit. B5) (no statistical testing)
Arnold et al., 1978 (77)	RCT	31, 5–12 years, 74% boys, MBD (a,b)	Mega-dose vit. B3, B5, B6, C and glutamate vs. similar tasting placebo powder for 2 weeks	Conners Scales and David’s Hyperkinetic Rating Scale	No significant difference on Conners Scales and David’s Hyperkinetic Rating Scale, (P and T)

RCT, randomized controlled trial; RDA, Recommended Daily Allowance; P, parents; T, teachers; O, observer; ADD-H, attention deficit disorder with hyperactivity; MBD, minimal brain dysfunction; CPT, Continuous Performance Test; CGI, Clinical Global Impression scale; CBCL, Clinical Behavior Checklist.

†Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

specific vitamins in “mega-doses”, many times above RDA (61, 77–79). One non-randomized (61) and one controlled study (78), which supplied mega-doses of different vitamins, reported an effect, but these studies have severe methodological limitations, such as lack of randomization, extremely short intervention periods and lack of statistical testing. Two more well-designed RCTs testing mega-doses of combinations of vitamins B3, B5, B6 and C, did not find any effect (77, 79). One of them reported deterioration in some ADHD symptoms after vitamin supplementation, and nearly half of the children developed elevated levels of liver enzymes when taking the vitamins, suggesting that the supplements may have a harmful effect (79). One small RCT found a positive effect of carnitine supplementation (80), but two larger RCTs did not find any effect (81, 82), although one did suggest a benefit to children with the inattentive subtype of ADHD (81).

Overall, there is no evidence that mega-dose vitamin supplementation ameliorate symptoms in children with ADHD. Moreover, studies indicate that megadoses of vitamins B3, B5, B6 and C combined may be liver toxic and should be discouraged.

MINERALS

We identified seven studies (Table 7) investigating the effect of mineral supplementation in children with ADHD: three RCTs focusing on zinc (83–85), two on iron (86, 87), and two on magnesium (88, 89). Two of the three double-blind RCTs of the effect of zinc supplementation found a significant positive effect on ADHD symptoms (83, 84), and one of them found that children with the lowest blood concentration of zinc and essential fatty acids benefited the most from the supplement. However, this study was limited by a high dropout rate, and the supplied dose of zinc (150 mg/day) was so high that it may have caused side-effects (84). The last study used a lower dose of zinc, which was increased halfway through the study (85). Although this did not result in any effect on ADHD symptoms, the group receiving zinc required a lower dose of central stimulating drugs (85). The two studies reporting an effect were carried out in Iran and Turkey, whereas the study that did not find any effect was from the USA where the prevalence of zinc deficiency may be lower.

In the studies with iron supplementation, a significant effect was only observed in a small uncontrolled intervention (86), whereas no effect on ADHD symptoms was found in the RCT, although a tendency towards improvement was found measured by Clinical Global Impression (87). This RCT was rather small and included children without anaemia, but with low iron stores (s-ferritin <30 mg/kg). Two studies with magnesium supplementation (88, 89) both reported improvement in ADHD symptoms, but both have severe methodological

problems, such as lack of randomization, and ADHD symptoms were not assessed by any known rating scale.

Based on these studies, there is no evidence to recommend zinc, iron or magnesium supplements to children with ADHD, but supplementation with zinc could be considered in areas with a high prevalence of zinc deficiency.

Conclusion

For most of the interventions regarding dietary components in children with ADHD, only few studies have been conducted, most with few participants and with a number of methodological flaws. These include problems concerning whether the rater was truly blinded (a parent involved in delivering the intervention may not be truly blinded), and old studies with uncertainty regarding the diagnostic classification as well as the psychometric qualities of the outcome measures used. Most studies did not mention whether the effect of dietary treatment depended on age, although a few studies found that artificial food colours had a more pronounced effect in the youngest (pre-school) children (32, 33). Thus, for most dietary interventions there is not enough evidence to recommend their routine use in clinical practice. There is some evidence that certain artificial food colorants may affect behaviour in children, but this effect is apparently not specific for children with ADHD. A few studies suggest that children with ADHD and sub-clinical deficiencies of zinc may benefit from supplementation.

Two types of interventions, Few Foods Diets and fish oil supplementation, seem to hold some promises with respect to reducing ADHD symptoms, but both need more thorough investigation before recommendations can be made. Few Foods Diets appear to have a consistently positive effect in the short-term in some children with ADHD. It is, however, not meant as a long-term treatment, but a diagnostic tool to identify children who are sensitive to certain foods. It is unknown what characterizes the types of food components that are problematic and few studies have assessed the effect of subsequent food challenges for more than a few weeks, and no studies have described the effect of the final diet. Several properly randomized and controlled trials have investigated the effect of fish oil supplementation, but the results are currently inconclusive with respect to the overall efficacy on ADHD symptoms. This may be explained by the low doses used in the studies, short intervention duration and lack of power. Meta-analysis of the fish oil RCTs tend to show some evidence for a small to modest effect and there are plausible biological mechanisms. Furthermore, fish oil-supplementation offers minimal inconvenience and no major side-effects.

Dietary alternatives in the treatment of ADHD patients are welcome, as the current pharmacological treatment is

Table 7. Studies assessing the effect of minerals on children with attention-deficit/hyperactivity disorder (ADHD) (or equivalent).

Reference	Design	n, age, sex, diagnosis [†]	Intervention	Outcome measure	Results (rater)
Arnold et al., 2011 (85)	RCT	52, 6–14 years, 84% boys, ADHD (a)	Zinc glycinate, 15–30 mg vs. control (not given) for 13 weeks (8 weeks without and 5 weeks with d-amphetamine)	Conners and SNAP-IV scales; MMF, CPT and Seat Activity tests	No significant difference on Conners and SNAP-IV scales (P and T) or MMF, CPT and Seat Activity tests
Konofal et al., 2008 (87)	RCT	23, 5–8 years, 77% boys, ADHD (a) + Non-anemic Ferritin < 30 ng/ml	Iron, 80 mg vs. identical tablets for 12 weeks	Conners and ADHD rating scales; GCI	No significant difference on Conners and ADHD rating scales (P and T), but significant effect on GCI; General improvement
Mousain-Bosc et al., 2006 (89)	Uncontrolled	40, 0–15 years, gender not given ADHD (a)	Magnesium, 180 mg + vit. B6, 18 mg for 0–6 months	No scales used	
Akhondzadeh et al., 2004 (83)	RCT	44, 5–11 years, 60% boys, ADHD (a)	Zinc sulphate, 55 mg vs. control (sucrose) for 6 weeks	ADHD rating scales	Significant beneficial effect of zinc on ADHD rating scales (P and T)
Bilici et al., 2004 (84)	RCT	400, 6–14 years, gender not given ADHD (c)	Zinc sulphate, 150 mg vs. control (sucrose) for 12 weeks	Conners, DuPaul Parent Ratings of ADHD and occasional developed scales	Significant beneficial effect of zinc on Conners, DuPaul Parent Ratings of ADHD and occasional developed scales (P and T)
Sever et al., 1997 (86)	Uncontrolled	14, 7–11 years, 100% boys, ADHD (a), Non-iron-deficient	Iron, 150 mg* for 1 month	Conners Scales	Significant improvement on Conners Scales (P, not T)
Starobrat-Hermelin & Koziol, 1997 (88)	Open, non-randomized controlled	75, 7–12 years, gender not given, ADHD (a)	Magnesium, 200 mg vs. “standard treatment” for 6 months	Conners Scales and Wender’s Scale of Behavior and the Quotient of Development to Freedom from Distractibility	Significant effect of magnesium on Conners Scales and Wender’s Scale of Behavior and the Quotient of Development to Freedom from Distractibility (P and T)

RCT, randomized controlled trial; GCI, Global Clinical Impression; P, parents; T, teachers; O, observer; SNAP-IV scale, Swanson, Nolan and Pelham rating scale; MMF, Matching Familiar Figures Test; CPT, Continuous Performance Test.

*Dose calculated based on child’s weight.

[†]Diagnosis based on: a = clinical examination, b = questionnaire, c = screening of non-diagnosed population for new cases followed by clinical examination, d = not given.

inefficient in some children with ADHD and may have problematic side-effects. It therefore seems worthwhile to continue research on diet, specifically to examine the long-term effect of restricted diets in sensitive children and to perform a sufficiently powered long-term trial with an appropriate dose of fish oil.

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